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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,874	TANHA ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/2/2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 5-40* is/are pending in the application.

4a) Of the above claim(s) *10-24 and 31-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-9 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3 and 5-40 are pending.

Claim 4 has been cancelled.

Claims 1, 5-8, 25 and 29 have been amended.

Claims 10-24 and 31-40 remain withdrawn from consideration.

2. Claims 1-3, 5-9 and 25-30 are under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

5. In order to have compact prosecution an Office Action can be performed on this application, however, this application contains claim amendments that are not in compliance with the Revised Amendment Practice under 37 CFR 1.121 as it applies to amendments filed on or after July 30, 2003. Specifically, cancelled claims, i.e., claim 4 may only have a "canceled" status identifier after the claim number. The text must not be supplied. Additional information on the revised amendment practice can be found on the USPTO website at:

http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/moreinfoamdtprac.htm.

Objections/Rejections Withdrawn

6. The objection to the disclosure for containing the incorrect page range for the Krebber reference is withdrawn in view of the amendment to the specification filed 9/2/2004.

7. The objection to claim 8 for reciting "absence of a tetracycline" is withdrawn in view of the amendment to the claim.

8. The rejections of claims 7-9 and 25-30, parts b-g, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the Applicant's arguments and amendments to the claims.

9. The rejection of claims 1-4 and 25-29 under 35 U.S.C. 102(b) as being anticipated by Casterman et al is withdrawn in view of the amendments to the claims and new grounds of rejection below.

10. The rejection of claims 1-4 and 25-29 under 35 U.S.C. 102(e) as being anticipated by Frenken et al [a] is withdrawn in view of the amendments to the claims and new grounds of rejection below.

11. The rejection of claims 1-4 and 25-29 under 35 U.S.C. 102(a) as being anticipated by Frenken et al [b] is withdrawn in view of the amendments to the claims and new grounds of rejection below.

12. The rejection of claims 1-9 and 25-30 under 35 U.S.C. 103(a) as being unpatentable over Casterman et al in view of McCafferty et al and Krebber et al is withdrawn in view of the amendments to the claims and new grounds of rejection below.

13. The rejection of claims 1-9 and 25-30 under 35 U.S.C. 103(a) as being unpatentable over Frenken et al [b] in view of McCafferty et al and Krebber et al is withdrawn in view of the amendments to the claims and new grounds of rejection below.

14. The rejection of claims 1-9 and 25-30 under 35 U.S.C. 103(a) as being unpatentable over Hoogenboom et al in view of Lauwereys et al and Krebber et al is withdrawn in view of the amendments to the claims and new grounds of rejection below.

Response to Arguments

15. The rejection of claims 1-9, part a, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The response filed 9/2/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that the term "derived" has been deleted and replaced with "cloned". In response to this argument still recites "llama antibodies derived from a non-immunized llama" and it is unclear how the llama antibodies are to be "derived" from a non-immunized llama to yield the class of derivatives referred to in the claims.

New Grounds of Rejections

16. Claims 5 and 6 are objected to as being dependent upon a cancelled claim.

Appropriate correction is required.

17. Claims1-3, 5-9 and 25-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-3, 5-9 and 25-30 are indefinite for reciting "said fragments comprising fragments..." in claim 1. Does the phrase "said fragments comprising fragments" mean

that the library of antigen-binding fragments are fragments of the antigen-binding fragments or does the phrase mean that some of the antigen-binding fragments in the library of antigen-binding fragments have the recited affinity or is some other meaning contemplated by the phrase?

b. Claims 5 and 6 are indefinite for reciting "10^9 clones" and "10^8 clones" in claims 5 and 6, respectively. The term "clones" means a population of cells formed by repeated division from a common cell. It is unclear what is contemplated by the phrase "10^9 clones" and "10^8 clones" because the size of phage libraries is measured in plaque forming units or pfu. Is the phage library made up of cells of identical genetic material (i.e., clones) formed by repeated division of a common cell or is the phage library a collection of phage, each encoding antigen-binding fragments having different sequence, specificity and affinity?

c. Claims 25-30 are indefinite for reciting "conventional heavy chain" in claim 25. What is contemplated by the phrase "conventional heavy chain"? What is a "conventional heavy chain"?

d. Claims 1-3 and 5-9 are indefinite for reciting "naïve phage display library of antigen-binding fragments" in claim 1. Are the antigen-binding fragments naïve in that that they have not been exposed to antigen or does the term "naïve" mean that the phage library is naïve?

e. Claims 1-3 and 5-9 are indefinite for reciting "antigen-binding affinity with a dissociation constant (Kd) of 5.7×10^{-5} M or lower Kd" in claim 1. The claims are unclear because the claims do not identify the specific antigen to which the claimed

antigen-binding fragments (i.e., antibody) bind. Affinity is a measurement of the attraction between an antibody and a specific antigen and it is unclear what antigen is being defined by the claimed affinity. What is the antigen to which the claimed antigen-binding fragments bind with an affinity with a dissociation constant of 5.7×10^{-5} M or lower.

18. Claims 1-3 and 25-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Casterman et al (WO 94/04678, 3/3/1994).

The claims are interpreted as being drawn to a naïve phage display library of llama antigen-binding antibody fragments obtained form a non-immunized llama comprising at least part of a VHH domain or a complete VHH domain, wherein some of the antigen-binding fragments in the phage display library have an antigen-binding affinity with a dissociation constant of 5.7×10^{-5} M or lower. The claims are also drawn to a cDNA library comprising nucleotide sequences encoding antigen-binding antibody fragments comprising at least part of a llama VHH domain or a complete llama VHH domain, wherein the cDNA is obtained by isolating lymphocytes from a non-immunized llama, isolating total RNA from the lymphocytes, reverse-transcribing the RNA and amplifying the cDNA sequences encoding the antigen-binding antibody fragments, cloning the amplified cDNA into a filamentous bacteriophage vector and recovering the obtained clones.

Caterman et al teach immunoglobulins devoid of light polypeptide chains (i.e., VHH), which include lama antibodies and the antibodies can be expressed by phage or

bacteriophage (see claims 1-2, 36 and page 9, in particular). Casterman et al teach that the immunoglobulins devoid of light polypeptide chains. Casterman et al teach "The preparation of antibodies can also be performed without a previous immunization of Camelids." (see page 24, lines 15-16, in particular). It is the Examiner's position that the phage display library of antigen-binding fragments taught by Casterman et al, produced from a non-immunized llama are naïve and the library necessarily comprises some antigen-binding fragments having an antigen-binding affinity with a dissociation constant of 5.7 X 10^{-5} M or lower when screened for antigen binding. Thus, it appears that Casterman et al have produced a phage display library of naïve antigen-binding fragments from a non-immunized llama that are identical to the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama with the phage display library of naïve antigen-binding fragments from a non-immunized llama of Casterman et al, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama and the phage display library of naïve antigen-binding fragments from a non-immunized llama of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

In addition, Casterman et al teach a cDNA library encoding a VHH obtained by (1) isolating lymphocytes from a biological sample from a Camelid (i.e., lama) without

previous immunization (see page 24, in particular), (2) isolating poly A RNA from the lymphoid cells; it is inherent that poly A RNA isolation is subsequent to the isolation of total RNA, (3) synthesizing cDNA using reverse-transcriptase, (4) amplifying the cDNA, (5) cloning the amplified sequence into a vector, and (6) recovering the clones (see page 21 and claim 38, in particular). Casterman et al teach filamentous bacteriophage vectors for cloning VHH antibodies (see page 24, in particular) and the VHH domains are "complete" since the are amplified with PCR primers in the promoter, leader or framework sequences for the 5' primer and the 3' primer is located in the hinge, CH2, CH3 or the 3' untranslated region or poly-A tail (see page 20, lines 5-13, in particular). For this rejection "comprising" is interpreted as open language meaning that the claims encompass additional elements including the isolation of poly A RNA, subsequent to the isolation of total RNA. Therefore, Casterman et al anticipate the claims.

Applicant's response filed 9/2/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that Casterman et al do not teach cDNA libraries based on camelid VHs. In response to this argument, claim 38 of Caterman et al specifically recites a cDNA library composed of nucleotide sequences coding for a heavy chain immunoglobulin that is "especially selected among the Camelids". The response also argues that Casterman et al does not disclose the preparation of heavy-chain antibodies by recombinant antibody/phage display technologies and teaches the preparation of heavy-chain monoclonal antibodies by hybridoma technology with prior immunization. In response to this argument, while Casterman et al does teach hybridoma technology for the preparation of heavy-chain antibodies, Casterman et al

also teach at page 24, lines 15-19 that the preparation of antibodies can also be performed without previous immunization of Camelids and the recourse to the technique of the hybridoma cell is not required. Clearly, Casterman et al teach a phage display library of camelid heavy-chain antibodies without previous immunization. Further, Casterman et al teach cloning the cDNA sequences encoding the heavy-chain antibodies into phages, especially filamentous bacteriophages.

19. Claims 1-3 and 25-29 are rejected under 35 U.S.C. 102(e) as being anticipated by Frenken et al [a] (U.S. Patent 6,399,763 B1, filed 1/19/2000).

The claims and their interpretation have been described supra.

Frenken et al [a] teach a phage display library of naïve antigen-binding antibody fragments comprising at least part of a heavy chain variable domain naturally devoid of light chains (i.e., VHH) obtained from a non-immunized llama and the antigen-binding affinities of some of the antibodies in the phage library have dissociation constants less than 100 nM, which is less than 5.7×10^{-5} M (see Example 1, column 5, lines 27-29 and column 9, lines 1-25). Frenken et al [a] teach 'full-length' VHH fragments, which are reasonably interpreted to be "complete" VHH domains (see column 5, lines 18-19 and Figure 1, in particular).

Frenken et al [a] also teach a cDNA library comprising nucleotide sequences cloned from a non-immunized lama, each nucleic acid encoding at least a part of a VHH antibody (see examples 1-3, in particular). Frenken et al [a] teach that the library of unimmunized lama antigen-binding antibody fragments are obtained by the steps

comprising (1) isolating lymphocytes from a biological sample obtained form a non-immunized lama (see column 9, lines 63-66, in particular), (2) total RNA was isolated from the lymphocytes (see column 5, lines 66-67, in particular), (3) performing first-strand cDNA synthesis (i.e., reverse-transcribing) and DNA encoding VHH fragments (i.e., cDNA) were amplified by PCR (see column 10, lines 4-5, in particular), (4) cloning the amplified VHH fragments into a vector (see column 10, lines 51-52, in particular), and (5) recovering the obtained clones (see column 10, lines 62-65 and Examples 2-3, in particular). Frenken et al [a] teach filamentous bacteriophage vectors (see column 8, lines 55-58, in particular). Thus, Frenken et al [a] anticipate the claims.

Applicant's response filed 9/2/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that Frenken et al [a] teach a synthetic antibody library and not a naïve antibody library and Frenken et al teach an expression library and not a display library as instantly claimed. In response to this argument Frenken et al [a] teach a naïve VHH phage display library from non-immunised llamas (see Example 1 and column 5, lines 27-29 and column 9, lines 1-25).

20. Claims 1-3 and 25-29 are rejected under 35 U.S.C. 102(a) as being anticipated by Frenken et al [b] (WO 99/37681, 7/29/1999).

The claims and their interpretation have been described supra.

Frenken et al [b] teach a phage display library of naïve antigen-binding antibody fragments comprising at least part of a heavy chain variable domain naturally devoid of light chains (i.e., VHH) obtained from a non-immunized lama (see Example 1 at page 13

and pages 11-12). Frenken et al [b] teach "complete" VHH domains (see Figure 1b and 1c, in particular). It is the Examiner's position that the phage display library of antigen-binding fragments taught by Frenken et al [b], produced from a non-immunized llama are naïve and the library necessarily comprise some heavy chain antibodies having an antigen-binding affinity with a dissociation constant of 5.7×10^{-5} M or lower when screened for antigen binding. Thus, it appears that Frenken et al [b] have produced a phage display library of naïve antigen-binding fragments from a non-immunized llama that are identical to the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama with the phage display library of naïve antigen-binding fragments from a non-immunized llama of Frenken et al [b], the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama and the phage display library of naïve antigen-binding fragments from a non-immunized llama of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Frenken et al [b] also teach a cDNA library comprising nucleotide sequences cloned from a non-immunized lama, each nucleic acid encoding at least a part of a VHH antibody (see examples 1-3, in particular). Frenken et al [b] teach that the library of a non-immunized lama antigen-binding antibody fragments are obtained by the steps

comprising (1) isolating lymphocytes from a biological sample obtained form a non-immunized lama (see page 13, lines 6-8, in particular), (2) total RNA was isolated from the lymphocytes (see page 13, lines 9-10, in particular), (3) performing first-strand cDNA synthesis (i.e., reverse-transcribing) and DNA encoding VHH fragments (i.e., cDNA) were amplified by PCR (see page 13, lines 11-14, in particular), (4) cloning the amplified VHH fragments into a vector (see pages 14, lines 26-28, in particular), and (5) recovering the obtained clones (see pages 14-15 and Examples 2-3, in particular) (see also pages 10-12 for above steps). Frenken et al [b] teach filamentous bacteriophage vectors (see page 11, lines 7-8, in particular). Thus, Frenken et al [b] anticipate the claims.

Applicant's response filed 9/2/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that Frenken et al [b] teaches a synthetic antibody library and not a naïve antibody library and is distinct from the naïve library instantly claimed and Frenken et al teach an expression library and not a display library as instantly claimed. In response to this argument Frenken et al [b] teach a naïve VHH phage display library from non-immunised llamas (see Example 1 and pages 11-12).

21. Claims 1-3, 5-9 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casterman et al (WO 94/04678, 3/3/1994) in view of McCafferty et al (U.S. Patent 6,172,197 B1, filed 6/7/1995) and Krebber et al (FEBS Letters, 377:227-231, 1995).

The claims are interpreted as drawn to a phage display library of naïve antigen-binding antibody fragments obtained form a non-immunized llama comprising at least part of a VHH domain or a complete VHH domain, wherein some of the antigen-binding fragments in the phage display library have an antigen-binding affinity with a dissociation constant of 5.7 X 10^{-5} M or lower and the size of the phage display library is at least 10^{9} and 10^{8} pfu/ml. Further, the vector for the phage display library is a fd-tet phage and the library is generated as plaques in the absence of tetracycline. The claims are also drawn to a cDNA library comprising nucleotide sequences encoding antigen-binding antibody fragments comprising at least part of a llama VHH domain or a complete llama VHH domain, wherein the cDNA is obtained by isolating lymphocytes from a non-immunized llama, isolating total RNA from the lymphocytes, reverse-transcribing and amplifying the cDNA sequences encoding the antigen-binding antibody fragments, cloning the amplified cDNA into a vector, which is a fd-tet filamentous bacteriophage and recovering the obtained clones.

Caterman et al have been described supra. It is the Examiner's position that the phage display library of antigen-binding fragments taught by Casterman et al, produced from a non-immunized llama are naïve and the library necessarily comprises some antigen-binding fragments having an antigen-binding affinity with a dissociation constant of 5.7 X 10^{-5} M or lower when screened for antigen binding. Thus, it appears that Casterman et al have produced a phage display library of naïve antigen-binding fragments from a non-immunized llama that are identical to the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama. Since the

Patent and Trademark Office does not have the facilities for examining and comparing the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama with the phage display library of naïve antigen-binding fragments from a non-immunized llama of Casterman et al, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama and the phage display library of naïve antigen-binding fragments from a non-immunized llama of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Casterman et al do not specifically teach phage display libraries of a size of at least 10^9 and 10^8 pfu/ml in claims 5 and 6, or a fd-tet phage vector in claim 7, or the phage display library generated as plaques in the absence of tetracycline in claims 8 and 9, or a cDNA library wherein the vector is fd-tet filamentous bacteriophage in claim 30. These deficiencies are made up for in the teachings of McCafferty et al and Krebber et al.

McCafferty et al teach phage display libraries for the expression of antibodies obtained from a non-immunized animal and the phage may be fd-tet filamentous bacteriophage or a derivative of fd-tet filamentous bacteriophage (see column 16, lines 21-23, 36-42, column 21, lines 2-7, Figure 3 and Example 1).

Krebber et al teach a chloramphenicol resistant (cam^R) and ampicillin resistant (amp^R) fd-tet phage having phage titers of at least 10^9 and 10^8 pfu/ml that were generated as plaques in the absence of tetracycline (see Figure 3b and Table 1).

Krebber et al teach that fd-tet phage carrying a tetracycline resistance gene in one of the hairpins of the phage origin of replication, yielded rather low phage titers (see page 228, right column), however, insertion of the ampicillin and chloramphenicol resistant genes individually into the fd-tet vector and selection with the appropriate antibiotic produced highly infective phage and high phage titers (see page 229, left column and Table 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a phage display library of naïve antigen-binding antibody fragments obtained from a non-immunized lama as taught by Casterman et al and to have used fd-tet filamentous bacteriophage (i.e., phage) as taught by McCafferty et al and to have generated the fd-tet phage display library in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a phage display library of naïve antigen-binding antibody fragments obtained from a non-immunized lama as taught by Casterman et al and to have used fd-tet filamentous bacteriophage (i.e., phage) as taught by McCafferty et al and to have generated the fd-tet phage display library in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al because Casterman et al teach phage display and cDNA libraries of antigen-binding antibody fragments from a non-immunized lama and McCafferty et al teach fd-tet filamentous bacteriophage for the expression of antibodies

obtained from a non-immunized animal and Krebber et al teach that fd-tet phage carrying a tetracycline resistance gene, yielded rather low phage titers, and higher phage titers (i.e., greater than 10^9 and 10^{10} pfu/ml) can be obtained using fd-tet phage generated in the absence of tetracycline. Therefore, it would have been obvious to the skilled artisan to use fd-tet phage generated in the absence of tetracycline in order to increase phage infectivity and produce higher phage titers in the non-immunized lama VHH phage display library taught by Casterman et al. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a phage display library of naïve antigen-binding antibody fragments obtained from a non-immunized lama as taught by Casterman et al and to have used fd-tet filamentous bacteriophage (i.e., phage) as taught by McCafferty et al and to have generated the fd-tet phage display library in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Applicant's response filed 9/2/2004 has been carefully considered, but is deemed not to be persuasive. The response argues as above, that Casterman et al only teach an immunized library and it would not have been obvious from Casterman that a naïve library could produce useful antigen binding fragments. In response to this argument and as argued above, while Casterman et al does teach hybridoma technology for the preparation of heavy-chain antibodies, Casterman et al also teaches at page 24, lines 15-19, that the preparation of antibodies can also be performed without previous

immunization of Camelids and the recourse to the technique of the hybridoma cell is not required and Casterman et al teach cloning the cDNA sequences encoding the heavy-chain antibodies into phages, especially filamentous bacteriophages. Clearly, Casterman et al teach a phage display library of camelid heavy-chain antibodies without a previous immunization. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

22. Claims 1-3, 5-9 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frenken et al [b] (WO 99/37681, 7/29/1999) in view of McCafferty et al (U.S. Patent 6,172,197 B1, filed 6/7/1995) and Krebber et al (FEBS Letters, 377:227-231, 1995).

The claims and their interpretation have been described supra.

Frenken et al [b] have been described supra. It is the Examiner's position that the phage display library of antigen-binding fragments taught by Frenken et al [b], produced from a non-immunized llama are interpreted to be naïve and the library necessarily comprises some antigen-binding fragments having an antigen-binding affinity with a dissociation constant of 5.7×10^{-5} M or lower when screened for antigen binding. Thus, it appears that Frenken et al [b] have produced a phage display library of naïve antigen-binding fragments from a non-immunized llama that are identical to the

claimed phage display library of naïve antigen-binding fragments from a non-immunized llama. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama with the phage display library of naïve antigen-binding fragments from a non-immunized llama of Frenken et al [b], the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama and the phage display library of naïve antigen-binding fragments from a non-immunized llama of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Frenken et al [b] do not specifically teach phage display libraries of a size of at least 10^9 and 10^8 pfu/ml in claims 5 and 6, or a modified fd-tet phage vector in claim 7, or the phage display library generated as plaques in the absence of tetracycline in claims 8 and 9, or a cDNA library wherein the vector is a fd-tet filamentous bacteriophage in claim 30. These deficiencies are made up for in the teachings of McCafferty et al and Krebber et al.

McCafferty et al have been described supra.

Krebber et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a phage display library of naïve antigen-binding antibody fragments obtained from a non-immunized lama as taught by Frenken et al [b] and to have used fd-tet filamentous bacteriophage (i.e., phage) as

taught by McCafferty et al and to have generated the fd-tet phage display library in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a phage display library of naïve antigen-binding antibody fragments obtained from a non-immunized lama as taught by Frenken et al [b] and to have used fd-tet filamentous bacteriophage (i.e., phage) as taught by McCafferty et al and to have generated the fd-tet phage display library in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al because Frenken et al [b] teach a phage display library of antigen-binding antibody fragments (and the encoding nucleic acids) comprising at least part of a heavy chain variable domain naturally devoid of light chains (i.e., VHH) obtained from a non-immunized lama and McCafferty et al teach fd-tet filamentous bacteriophage for the expression of antibodies obtained from a non-immunized animal and Krebber et al teach that fd-tet phage carrying a tetracycline resistance gene, yielded rather low phage titers, and higher phage titers (i.e., greater than 10^9 and 10^{10} pfu/ml) can be obtained using fd-tet phage generated in the absence of tetracycline (see Table 1). Therefore, it would have been obvious to the skilled artisan to use fd-tet phage in the absence of tetracycline in order to increase phage infectivity and produce higher phage titers in the non-immunized lama VHH phage display library taught by Frenken et al [b]. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a phage display library of naïve antigen-

binding antibody fragments obtained from a non-immunized lama as taught by Frenken et al [b] and to have used fd-tet filamentous bacteriophage (i.e., phage) as taught by McCafferty et al and to have generated the fd-tet phage display library in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Applicant's response filed 9/2/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that Frenken et al [b] disclose only an expression library and fail to provide antibody fragments with useful affinity for their target. In response to this argument and as argued above, Frenken et al [b] teach a naïve VHH phage display library from non-immunised llamas (see Example 1 at page 13 and pages 10-12). VHHs from a non-immunised source are reasonably interpreted to be naïve in that the VHHs have not been exposed to antigen. Further, Frenken et al [b] teach that the VHH antibodies were highly active and exhibited strong antigen specific recognition and the naïve VHH phage display library from non-immunised llamas taught by Frenken et al [b] would necessarily comprise some antigen-binding fragments having an antigen-binding affinity with a dissociation constant of 5.7×10^{-5} M or lower when screened for antigen binding. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

23. Claims 1-3, 5-9 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogenboom et al (Immunotechnology 4:1-20, 1998) in view of Lauwereys et al (The EMBO Journal, 17(13):3512-3520, 1998) and Krebber et al (FEBS Letters, 377:227-231, 1995).

The claims and their interpretation have been described supra.

Hoogenboom et al teach phage display antibody libraries from non-immunized animal sources, such as the V-genes from lymphoid cells to create a naïve repertoire of rearranged genes (see page 5, right column, in particular). Hoogenboom et al teach that antigen-biased IgG V-genes should be avoided (see page 5, right column, in particular). Hoogenboom et al teach cDNA libraries encoding antibodies from a non-immunized animal source comprising the steps of isolating lymphocytes, isolating RNA for the lymphocytes, synthesizing cDNA and amplifying the cDNA by PCR, cloning the amplified cDNA into a vector and recovering the obtained clones (see pages 5-6 and Figure 3, in particular). Hoogenboom et al also teach the fd-tet vector (see page 3, left column, in particular). Additionally, Hoogenboom et al teach the construction of an antibody phage library following immunization of a camel, however, Hooogenboom et al admits that immunization is not always possible due to ethical constraints, neither always effective due to tolerance mechanisms towards or toxicity of antigen (see page 5, left column, in particular). Hoogenboom et al teach that phage display libraries of

naïve antibodies that are sufficiently large and diverse can be used to generate antibodies to a large panel of antigens, including self, non-immunogenic and toxic antigens (see page 6, left column, in particular). Hoogenboom et al do not specifically teach a cDNA antibody library or phage display library of antigen-binding antibody fragments obtained from a non-immunized llama comprising at least part of a VHH domain or a complete VHH domain and the size of the phage display library is at least 10^9 and 10^8 pfu/ml or a fd-tet phage display library generated in the absence of tetracycline. These deficiencies are made up for in the teachings of Lauwereys et al and Krebber et al.

Lauwereys et al teach that heavy chain antibodies devoid of light chains (i.e., VHH) can be obtained from llamas and these heavy chain antibodies have acquired the potential to recognize protein cavities and as such the ability to inhibit enzymes (see page 3512, right column, in particular). Lauwereys et al teach that VHH antibodies posses superior properties such as simple isolation, high solubility and stability and are advantageous for intracellular immunization (see page 3518, left and right columns, in particular). Lauwereys et al teach the single-domain nature of the VHH antibodies avoids the introduction of essential linkers used in scFv constructs, which might lead to aggregation or susceptibility to proteolysis and it is likely that VHH antibodies are more feasible for intracellular immunization compared to conventional scFvs due to their superior enzyme-neutralizing capacity (see page 3518, right column, in particular).

Krebber et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a phage display library of VHH antibodies as potent enzyme inhibitors as taught by Lauwereys et al and to have obtained the VHH antibodies from a non-immunized llama (i.e., naïve VHH) since immunization is not always ethically possible, nor always effective for non-immunogneic and toxic antigens as taught by Hoogenboom et al and it would have been obvious to have used fd-tet phage in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a phage display library of VHH antibodies as potent enzyme inhibitors as taught by Lauwereys et al and to have obtained the VHH antibodies from a non-immunized llama (i.e., naïve VHH) since immunization is not always ethically possible, nor always effective for non-immunogneic and toxic antigens as taught by Hoogenboom et al and it would have been obvious to have used fd-tet phage in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al because Hoogenboom et al teach al teach cDNA libraries and phage display libraries of antibodies from non-immunized animal sources and immunized sources are not always ethically possible, neither always effective due to tolerance mechanisms towards or toxicity of antigen and phage display libraries of naïve antibodies that are sufficiently large and diverse can be used to generate antibodies to a large panel of antigens, including self, non-immunogenic and toxic antigens and Lauwereys et al teach that VHH antibodies obtained from llamas are

potent enzyme inhibitors and are better suited for intracellular immunization compared to conventional scFvs due to their superior enzyme-neutralizing capacity. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a phage display library of VHH antibodies as potent enzyme inhibitors as taught by Lauwereys et al and to have obtained the VHH antibodies from a non-immunized lama (i.e., naïve VHH) since immunization is not always ethically possible, nor always effective for non-immunogneic and toxic antigens as taught by Hoogenboom et al and it would have been obvious to have used fd-tet phage in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al because Hoogenboom et al and Krebber et al teach fd-tet phage and Krebber et al teach that fd-tet phage carrying a tetracycline resistance gene, yielded rather low phage titers, and higher phage titers (i.e., greater than 10^9 and 10^{10} pfu/ml) can be obtained using fd-tet phage generated in the absence of tetracycline (see table 1). Therefore, it would have been obvious to the ordinary skilled artisan to generate a phage display library in the absence of tetracycline to obtain higher phage titers because phage display libraries of naïve antibodies that are sufficiently large and diverse can be used to generate antibodies to a large panel of antigens, including self, non-immunogenic and toxic antigens. Further, it would have been obvious to by-pass immunization since immunized sources are not always ethically possible, nor always effective towards non-immunogenic and toxic antigens. Additionally, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that a phage display library of antigen-binding fragments prepared from a non-

immunized llama would necessarily comprise some naïve antigen-binding fragments having an antigen-binding affinity with a dissociation constant of 5.7 X 10^{-5} M or lower when screened for antigen binding. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama with the phage display library of naïve antigen-binding fragments from a non-immunized llama of the prior art, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed phage display library of naïve antigen-binding fragments from a non-immunized llama and the phage display library of naïve antigen-binding fragments from a non-immunized llama of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a phage display library of VHH antibodies as potent enzyme inhibitors as taught by Lauwereys et al and to have obtained the VHH antibodies from a non-immunized llama (i.e., naïve VHH) since immunization is not always ethically possible, nor always effective for non-immunogneic and toxic antigens as taught by Hoogenboom et al and it would have been obvious to have used fd-tet phage in the absence of tetracycline for higher phage library titers (i.e., greater than 10^9 pfu/ml) as taught by Krebber et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Applicant's response filed 9/2/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that with respect to the Hoogenboom reference, there are significant differences between VHs and VHHs, particularly with respect to their typical binding affinities and to apply Hoogenboom's approach (developed for higher affinity VHs) to the production of a library of VHHs from a non-immunised animal would not have been successful, due to the low binding affinity observed in such a system. In response to these arguments, Applicants arguments are not commensurate in scope with the claim because the claims are drawn to a variable heavy domain (VHH or VH). Further, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references as a whole would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusions

24. No claim is allowed.

25. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER